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Bo Lilja

Regional Lung Perfusion and Central Haemodynamics in Man

With special reference to time, body
position, lung volume, breath-holding,
hypoxia, and hyperoxia

Malmö 1972

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Like all research work the present study has depended upon the generous advice and kind assistance of many friends whom I thank cordially.

Bo Lilja

The present thesis is based on the following publications:

- I Regional lung function and central haemodynamics in man during two hours of sitting. Scand. J. clin. Lab. Invest. Submitted for publication.
- II Pulmonary blood flow distribution at different lung volumes and body positions. Scand. J. clin. Lab. Invest. Submitted for publication.
- III Haemodynamic changes at different lung volumes. Scand. J. clin. Lab. Invest. Submitted for publication. Together with M. Arborelius, Jr.
- IV Effect of sitting, hypoxia, and breath-holding on the distribution of pulmonary blood in man. Scand. J. clin. Lab. Invest. 24, 261, 1969. Together with M. Arborelius, Jr.
- V The distribution of pulmonary blood flow in man during oxygen breathing and breath-holding. Scand. J. clin. Lab. Invest. 26, 105, 1970.
- VI Regional lung function and central haemodynamics during hypoxia, hyperoxia and breath-holding. Scand. J. clin. Lab. Invest. Submitted for publication.

These papers will be referenced in the text as I, II, III, IV, V and VI.

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Symbols and abbreviations

RV	=	residual volume
FRC	=	functional residual capacity
TLC	=	total lung capacity
Ind. Q	=	perfusion index, i.e. perfusion per unit lung volume at FRC
Ind. V	=	ventilation index, i.e. ventilation per unit lung volume at FRC
$\dot{Q}$	=	cardiac output
PaO_2	=	oxygen tension in arterial blood

Statistics

Common statistical methods as described by Bradford Hill (16) were used.

$\bar{d}$	=	mean difference between paired data
r	=	correlation coefficient
P	=	probability
S.E.	=	standard error

GENERAL INTRODUCTION

Bronchspirometry (15) made it possible to evaluate the function of each lung separately. The usefulness of this method in pulmonary circulation research is well documented. Reviews of the literature in this field have been presented by Svanberg (48) and Arborelius (2).

Radioactive gases, such as $C^{15}O_2$, $^{15}O_2$ and ^{133}Xe , permitted the study of the regional lung perfusion within each lung during different experimental conditions (10, 23, 53). The regional circulation of the lung can also be studied by radioactive particles, such as macro-aggregated albumin tagged with Iodine-131 ($MAA^{131}I$) (50). However, ^{133}Xe was preferred in the present study since its rapid elimination through the lung allowed repeated measurements during a single investigation. Furthermore, the radioactive dose can be kept low and the perfusion be related to ventilation and lung volume. In addition, good agreement has been found between our ^{133}Xe method and bronchspirometry as regards measurements of distribution of perfusion, ventilation and vital capacity (42).

In erect man, due to gravitational forces, the lung bases are better perfused than are the lung apices (10, 53). Since the perfusion of the lung bases increases more than ventilation when changing body position from supine to erect, the bases will be overperfused as compared to ventilation (10). It is not known whether the basal hyperperfusion persists or if it is modified during prolonged sitting, and to what extent it is accompanied by changes in central haemodynamics. Furthermore, data on central haemodynamics are scarce

from seated normal subjects (13).

In the erect position the pressure-flow characteristics of the pulmonary blood flow have been described by Permutt, Bromberger-Barnea & Bane (45) and in experiments on isolated erect dog lungs West, Dollery & Naimark (54) distinguished three zones. The extension of each of these zones could be determined if the pulmonary artery, alveolar and pulmonary venous pressures were known. In the first (apical) zone alveolar pressure exceeds pulmonary arterial pressure, which prevents flow. In the second (middle) zone pulmonary artery pressure exceeds alveolar pressure which exceeds pulmonary venous pressure and the driving pressure is the difference between the arterial and alveolar pressures. The flow will increase down the lung as this difference increases. In the third zone, where both the pulmonary artery pressure and pulmonary venous pressure exceed alveolar pressure, the driving pressure will be the difference between the pulmonary arterial and venous pressures. From experiments in man a fourth zone located just above the diaphragm has been described (31, 32). The driving pressure here is difficult to define as it is presumed to be influenced by interstitial pressure.

In the erect position the influence of different lung volumes on pulmonary blood flow distribution was analysed by Anthonisen & Milic-Emili (1). They found that the apical blood flow increased at residual volume as compared to the distribution found at functional residual capacity and total lung capacity and that almost the whole lung was covered by zone 3. The regional perfusion is usually registered either at TLC or at FRC (10, 42). It is thus important to know the normal

distribution of perfusion at different lung volumes and to correlate the changes in perfusion to the changes in central haemodynamics. In man only one attempt has been reported (1).

Even though gravity is the main cause for uneven distribution of perfusion in the erect position, it can be opposed e.g. by hypoxia (2, 27) and exercise (9, 17). It has been presumed that basal hypoxia or other regional factors may decrease the hyperperfusion of the bases, thus making the lungs more effective for gas exchange (27, 52). Furthermore, it is known that hypoxia produces changes in the central haemodynamics (25), but simultaneous measurements of regional perfusion and central haemodynamics during hypoxia have not been performed.

The aim of the present study was to:

- (1) Define whether or not the distribution of pulmonary blood flow changes with time in the sitting position (I).
- (2) Analyse how the distribution of pulmonary blood flow is influenced by different lung volumes (II & III).
- (3) Analyse whether or not the distribution of pulmonary blood flow is influenced by active mechanisms (IV, V & VI).
- (4) Analyse how any observed changes in distribution of pulmonary blood flow are correlated to changes in central haemodynamics (I, III & VI).

CALCULATIONS AND METHODS

The $^{133}\text{Xenon}$ method. The use of $^{133}\text{Xenon}$ as a tracer for

determination of ventilation is first mentioned in the investigations of Knipping, Bolt, Venrath, Valentin, Ludes & Endler (34). Methods for measurements of both regional perfusion and ventilation with $^{133}\text{Xenon}$ were presented by Ball, Stewart, Newsham & Bates (10) and Dollery, Hugh-Jones & Matthews (19). In 1968 Miörner (42) presented an investigation where the lung volumes, ventilation and perfusion of each lung were determined both with a $^{133}\text{Xenon}$ method, radiospirometry, and bronchosprometry. In this investigation four pairs of scintillation detectors were used and thus each lung was divided into one apical and one basal field. The percentage of the perfusion and ventilation going to the right lung was the same whether determined with radiospirometry or bronchosprometry. In the present investigations the same type of collimation system was used, but in order to achieve a lighter and mobile apparatus only four detectors were employed either on the back or on the front of the thorax.

The technical equipment used has been described elsewhere (4). It consists of four integral line scintillation detectors with crystals 50×5 mm (Isotopes Inc., St-85-I, Westwood, USA) and four ratemeters with discriminator units and high voltage power supply. The discriminators were set to cut out radiation below about 75 keV, thus reducing scatter radiation. The thin crystal used has a low sensitivity for high energy radiation which reduces background activity. The activity from each detector was recorded on a four-channel light-beam oscillograph and on a tape recorder. The tape was replayed and analysed with the equipment described by Miörner (42). The collimation system can be altered by changing the form of the lead shields at the end of the cylindrical lead collimator or the distance

crystal to front opening. Two types of collimation systems have been used in the present investigation. The counting fields of the detectors presented in paper IV are used only in that investigation. In the other papers, in order to have better separation between the apical and basal fields, the vertical distance between the centres of the crystals was increased and the position of the lead shields changed. The counting fields of the detectors thus derived are presented in paper V.

The disadvantage with this detector arrangement is that local changes in perfusion gradient down the lung cannot be detected. However, the wide collimation will directly yield the mean perfusion per lung volume in the large apical and basal regions, and even large changes in perfusion per lung volume in small regions will be taken into account only in relation to their volume, i.e. to their physiological importance. Also the amount of $^{133}\text{Xenon}$ necessary to provide an acceptable statistical variation was less with two wide fields over each lung than when using several narrow collimators.

With detectors on one side of the thorax, it has been shown (5) that there is a tendency to overestimate the perfusion of the right lung with ventral detectors alone and to underestimate it with only dorsal detectors as compared with measurements made with both ventral and dorsal detectors. In all presented investigations in the sitting and supine positions the two apical fields are summed as are the basal fields. The influence of the heart (5) can in the present studies be neglected as it affects volume and perfusion to the same degree and thus does not change the perfusion per unit lung volume.

Xenon-133 is an inert gas with low solubility in body fluids, the Bunsen coefficient for human whole blood being 0.149 ± 0.006 (44). It was delivered by AB Atom-energi, Studsvik, Sweden, as a gas or dissolved in saline. The half-life of $^{133}\text{Xenon}$ is 5.27 days. The isotope decays to stable cesium, emitting beta-particles of a maximum energy of 347 keV. The nucleus thus formed reaches a stable state either by emitting gamma-ray of an energy of 81 keV or by the process of internal conversion, which is accompanied by the emission of X-rays of an energy of approximately 30 keV (10).

Radiation doses. According to the tissue radiation doses given by Lassen (35), the highest values will be found in paper I where the tracheal mucosa received about 210 mrad and the gonads about 3 mrad. These values are lower than the highest allowed weekly dose for persons in radiological work according to the International Commission on Radiological Protection (I.C.R.P.).

Regional blood flow and ventilation. In agreement with the results of others (9, 17), there were no circulatory or ventilatory differences between the right and left apical fields or between the left and right basal fields. Therefore pulses from the two apical detectors were added as were those from the basal detectors. In papers I, IV, V and VI the regional perfusion, ventilation and lung volumes were calculated according to Miörner (42). The count rates in each region, i.e. the two apices and the two bases, were expressed as percentages of the sum of the count rates in the four regions. The percental count rate following the injection was divided by the percental count rate following the rebreathing and an index of perfusion (Ind. Q) was formed, expressing the perfusion per unit volume. The ventilation index (Ind. V)

was derived in a similar way by dividing the percental count rate following the second or third inhalation by the percental count rate following the rebreathing. In paper IV the perfusion and ventilation gradients were calculated from Ind. Q and Ind. V according to Dugard & Naimark (22). In order to enable comparison with the results obtained by Anthonisen & Milic-Emili (1) and Hughes, Glazier, Maloney & West (31, 32), the perfusion was expressed as perfusion per alveolus in papers II and III.

Indices Q and V used here and by Miörner (42) and Mannell, Prime & Smith (39) are not identical with the "distribution indices" described by Ball et al. (10). Neither is index Q per alveolus identical with that used by Anthonisen & Milic-Emili (1), who compared a calculated concentration in each lung region to an ideal even concentration in the same region. With Miörner's method (42) an index in one region cannot increase without a concomitant decrease in another region. With this method the average of all indices is 1.00 or 100 %, but with the method of Ball et al. (10) it might occur that no region achieves 100 % per unit volume (10). Good reproducibility was found with the $^{133}\text{Xenon}$ method (42) and the methodological errors have been discussed by several workers (10, 17, 38, 42) and summarized by Bake (6).

Catheterization. With the Seldinger technique (46) polyethylene catheters (PE 160, Intramedic[®], Clay Adams, New York, USA) were introduced, and pressures were obtained from the brachial artery, the pulmonary artery and the right atrium. The $^{133}\text{Xenon}$ was injected into the right atrium and arterial blood gases obtained from the brachial artery. For simultaneous measurements

of wedge pressure and pulmonary artery pressure a double lumen catheter (Cournand 9) was used. The position of all intrathoracic catheters was controlled with fluoroscopy. For intravascular pressures the following zero reference points were used: in the supine position a level of 5 cm behind the sternum; in the sitting position the 4th costal interspace at the sternum; in the lateral position the midline of the sternum. All pressures were recorded with conventional equipment (Electromanometer, EMT 35, Mingograph 81, AB Elema-Schönander, Stockholm, Sweden). Mean pressures were obtained by electrical damping.

Oesophageal pressure was determined by an air-filled polyethylene catheter, 3 mm in diameter. The distal end was covered with a 10 cm long thin-walled rubber balloon, 5 mm in diameter. The pressures were registered with the same equipment as the intravascular pressures.

Cardiac output was measured by a dye (bromsulphalein) dilution method (51) and central blood volume was determined according to Hamilton, Moore, Kinsman & Spurling (29).

Arterial blood gas tensions and pH were measured with conventional electrodes (Instrumentation Laboratory Inc., Boston, USA and Radiometer, Copenhagen, Denmark).

Regional lung perfusion and central haemodynamics during prolonged sitting (I)

I n t r o d u c t i o n

In the supine or prone positions the perfusion is almost evenly distributed between apices and bases, while in the erect position the pulmonary blood flow distribution is uneven and more blood passes through the lung bases than through the apices (10, 33, 53). That the change in distribution of perfusion was not immediate after changing body position but instead happened gradually was shown in one subject by Bryan, Bentivoglio, Beerel, MacLeish, Zidulka & Bates (17). A decrease was found in apical perfusion following 15 minutes of standing as compared with the value obtained immediately after standing.

In the sitting position a similar gradual decrease in apical perfusion has been noted (9, IV & V). However, in these studies the distribution of perfusion was not measured often enough to illustrate the early change in distribution with time. Neither were eventual changes with time in central haemodynamics measured.

M a t e r i a l a n d m e t h o d s

Ten healthy men (age 24 - 40) volunteered. The regional distribution of perfusion, ventilation and lung volume was estimated with dorsal detectors in the prone position (five subjects) and during two hours of sitting (ten subjects). All subjects were resting in the prone or supine position for 10 minutes before sitting up. Simultaneously with the regional lung function, the

pulmonary artery pressure (five subjects), cardiac output and arterial blood gases (eight subjects) were measured.

R e s u l t s a n d d i s c u s s i o n

In the five subjects where the regional perfusion was measured in the prone position, an even distribution was registered with an apical perfusion index of 1.01 and a ventilation index of 1.00. These values approximate earlier results in the supine position (42). When the regional perfusion was again measured after 1 minute in the sitting position, the Ind. Q of the apices had decreased and subsequent estimates after 3, 6 and 10 minutes showed a successive decrease in all ten subjects. In half of the subjects there was then no further decrease in apical perfusion, while in the other half the lowest values were noted after 20 minutes. During the last 90 minutes the Ind. Q of the apices did not decrease further and showed only small, insignificant variations. The results indicate that the decrease in perfusion of the apices that occurs when changing body position from supine or prone to sitting can be divided into one rapid and one slow phase. The rapid phase commonly took place within the first minute of sitting, while the slower phase was terminated after 10 to 20 minutes. If the apical Ind. Q in the supine or prone position is assumed to be 1.0 about 60 % of the total decrease in apical perfusion occurred during the first minute.

For technical reasons it was impossible to determine ventilation as often as perfusion. The apical Ind. V had decreased after 10 minutes in the sitting position compared with that found in the prone position, but

was less pronounced than the decrease in Ind. Q.

The $\dot{Q}$ also decreased with time as did central blood volume and a statistically significant positive correlation ($r = 0.48$; $P < 0.01$) was found between the changes in apical perfusion index and changes in $\dot{Q}$ during the whole period of sitting. The absolute and percental decrease in perfusion calculated in litres per minute mainly occurred in the apical region. The changes in $\dot{Q}$ and central blood volume indicate a redistribution of blood away from the lungs and thorax, such as has been described during fainting (17). However, five of the subjects who did not differ from the rest of the group as regards changes in Ind. Q, showed no decrease in brachial artery pressure and none of the ten subjects showed any tendency to faint.

During the second phase (1 to 20 minutes in sitting) a decrease in pulmonary artery pressure and $\dot{Q}$ was found, and when the changes in apical perfusion index and the changes in mean pulmonary artery pressure were compared, a statistically significant positive correlation ($r = 0.69$; $P < 0.01$) was found. The pulmonary artery pressure then increased again and the changes in pulmonary artery pressure during the last 90 minutes of sitting were not significantly related to the changes in Ind. Q of the apices. The mechanism underlying this late increase in pulmonary artery pressure is obscure. It was unaccompanied by any increase in $\dot{Q}$. It seems probable that it is due to a general pulmonary vasoconstriction, since a preferential basal vasoconstriction should result in a measurable redistribution of blood towards the apices (27).

The changes in perfusion during the first rapid phase are probably mainly due to the influence of gravity on intrapulmonary blood distribution. During the second phase it might be hypothesized that the changes in the regional perfusion of the lung might be explained by the changes in $\dot{Q}$ alone. To test this hypothesis it is necessary to know the left atrial pressure. The end-diastolic pulmonary artery pressure has been shown to equal left atrial pressure in normals (26). If pulmonary vascular resistance had remained stable, the $\dot{Q}$ should have decreased about 3 litres between the first and twentieth minute measurements to account for the observed decrease in mean pulmonary artery pressure. The decrease in $\dot{Q}$ was after 30 minutes 1.5 litres and thus a decrease in pulmonary vascular resistance can be presumed to have occurred during the first 20 minutes of sitting. Thereafter the pulmonary vascular resistance was close to or higher than that measured at 1 minute.

In papers IV and V it was proposed that the increase in basal perfusion, if not accompanied by an increase in ventilation, should give a basal hypoxia and thus a basal vasoconstriction. However, there was no decrease in PaO_2 , and in the only subject where ventilation was measured, both total and alveolar ventilation increased. Therefore, it appears unlikely from this single experiment and from the blood gases studied that vasoconstriction due to hypoxia would develop during prolonged sitting. It can be deduced from earlier investigations (2) that the alveolar oxygen tension must be below 70 mm Hg before measurable vasoconstriction occurs. In the presented results the mean PaO_2 was above 90 mm Hg during the whole investigation and thus even at the bases the oxygen tension was probably not low enough to cause significant vasoconstriction.

Regional lung function and central haemodynamics at different lung volumes and body positions (II & III)

I n t r o d u c t i o n

Using the $^{133}\text{Xenon}$ method for determination of perfusion Ball et al. (10) and Bryan et al. (17) confirmed the results by West & Dollery (53), who found a linear increase in perfusion from apex to base. According to Anthonisen & Milic-Emili (1) this results from expressing perfusion as flow per unit volume. Milic-Emili, Henderson, Dolovich, Trop & Kaneko (41) have shown that when the lung is in the erect position, the alveoli decrease in volume down the lung which in itself gives an increase in flow per lung volume even if the perfusion per alveolus was uniform throughout the lung.

Anthonisen & Milic-Emili (1), using a method where the perfusion per alveolus could be calculated, found that in the sitting position the apical perfusion increased at RV as compared with FRC. They drew the conclusion from their experimental data that at full inspiration the pulmonary artery pressure must have increased and the pulmonary venous pressure decreased or remained the same as measured at FRC. At maximal expiration the pulmonary venous pressure must have risen sharply. Anthonisen & Milic-Emili (1) also measured the pulmonary artery pressure simultaneously with the wedge pressure in one subject, and the pressures found confirmed their above mentioned calculations. Apart from this single pressure measurement in the sitting position, there are no reports of simultaneous measurements of regional lung function and central haemodynamics at different lung volumes. As hydrostatic pressure differ-

ences are almost negligible in the supine and right lateral body positions in the apico-diaphragmatic direction, the influence of breathing manoeuvres in these two body positions on the distribution of pulmonary blood flow was also studied in order to obtain a better understanding of the influence of other factors than gravity.

M a t e r i a l a n d m e t h o d s

Five healthy women (age 19 - 23) and twenty-four healthy men (age 20 - 37) volunteered. The regional distribution of perfusion was studied at RV, FRC and TLC in the supine, sitting and right lateral body positions. The pulmonary artery pressure, $\dot{Q}$ and arterial blood gases were also measured under the same experimental conditions. In four subjects simultaneous measurements of wedge pressure and pulmonary artery pressure were performed.

R e s u l t s a n d d i s c u s s i o n

Although the four lung zones (31, 32) cannot be distinguished with the present detector arrangement, the principal changes in perfusion that have been described (1, 31, 32) to occur when the lung volume changed from FRC to RV in the sitting position were verified.

Independent of body positions, the pressure changes in the pulmonary artery were almost the same (Fig. 1). There was no significant change in pressure during breath-holding at FRC. During the exhalation to RV the pulmonary artery pressure increased and reached a maximum within 3 seconds after the exhalation was ended. The pressure then decreased and levelled off slightly above the value registered before exhalation. When

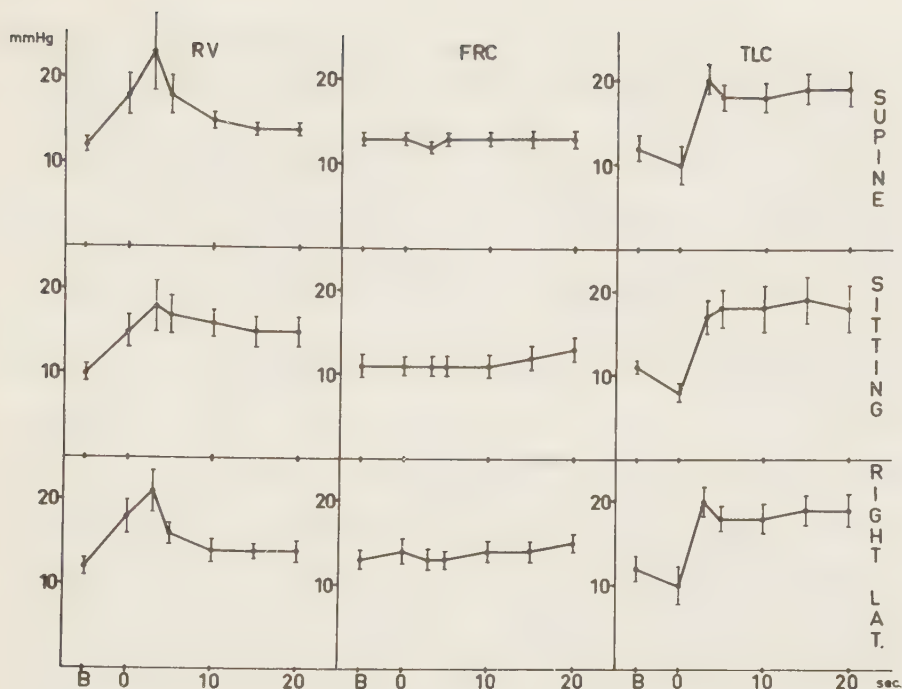


Fig. 1 Mean pulmonary artery pressure in the supine (six subjects), sitting (ten subjects) and right lateral (seven subjects) body positions at RV, FRC and TLC before (B) and during 20 seconds of breath-holding. Mean values $\pm$ S.E. are shown.

performing the TLC manoeuvre the pulmonary artery pressure decreased during inhalation but as soon as TLC was reached the pressure increased again and levelled off above the initial value.

In the supine position the pulmonary capillaries may be almost maximally distended according to Gurtner &

Fowler (28), which should limit the possibility for changes in the even distribution found at FRC. Changes in distribution of blood flow due to gravitational force will not be detected as this force is parallel to the axis of the detectors. A slight but insignificant increase in apical perfusion was, however, registered at TLC and is in agreement with earlier results (17). This phenomenon probably depends on the fact that at TLC, due to the movement of the thoracic cage, parts of the basal regions are located higher than the apical ones and thus cause a hydrostatic pressure difference.

In the sitting position the distribution of perfusion was more even at RV than at FRC, which is in agreement with earlier results (1, 31, 32). However, if the injection of $^{133}\text{Xenon}$ was delayed 10 seconds following the exhalation when the pulmonary artery pressure had levelled off (Fig. 1), the distribution of perfusion was less even compared to if the injection was done immediately, and did not significantly differ from the distribution found at FRC. When the wedge pressure was measured in the basal region at RV it was commonly as high or even higher than the systolic pulmonary artery pressure. This probably does not indicate reversed basal circulation. It is more likely that the registered increase in the wedge pressure is affected by alveolar pressure. As there is no blood flow through the vessel where the wedge pressure is registered, an increased resistance due to knicking cannot influence the pressure while an increased intra-alveolar pressure both can collapse intra-alveolar vessels and thereafter cause the pressure increase. It is known that "airway closure" occurs at low lung volumes in the basal regions (41). The wedge pressure registered higher up in the lung was

not increased above the pulmonary artery pressure at RV. It thus seems probable that increased vascular resistance, secondary to increased intra-alveolar pressure in closed off lung regions at the base, may be an important factor for explaining the decrease in basal blood flow at RV. Furthermore, there seems to be a rapid haemodynamic adaptation as indicated by the tendency for pulmonary artery pressure and pulmonary blood flow distribution to approach with time the values measured at FRC.

The pressure increase measured at TLC was not accompanied by any increase in apical perfusion. On the contrary, the perfusion was more uneven than at FRC and did not change even when the injection was delayed for 10 seconds. This increase in pulmonary artery pressure with decreasing apical perfusion is paradoxical and is probably caused by an increase in resistance throughout the lung, eventually combined with a preferential increase in apical resistance as a preferential basal vasoconstriction should give a more even distribution of perfusion (27). However, the hydrostatic pressure difference between apex and base will increase at a maximal inhalation and this condition will counteract the effect of the increase in pulmonary artery pressure.

In the right lateral position the difference in perfusion between the upper and lower lung remained almost the same whether the measurements were made at RV or FRC, while the perfusion of the lower lung was greater at TLC than at RV.

Kaneko, Milic-Emili, Dolovich, Dawson & Bates (33) calculated from their experimental data that the lower two thirds (≈ 18 cm) of the lungs were in zone 3.

Furthermore, during an expiration from FRC to RV more air is exhaled from the upper than from the lower lung (48, 49). The interstitial pressure of the upper lung should then increase more than in the lower lung and thus counteract a redistribution towards the upper lung. The delayed injection of $^{133}\text{Xenon}$ at RV also provided values close to the initial ones, which indicates that the perfusion of the superior lung in relation to the lower one is little affected by pulmonary artery pressure variations.

The lowermost lung in the lateral position has lower FRC than does the upper lung, the former being closer to RV (48). The change in distension of the lung tissue between FRC and RV will be small in the lower lung but large in the upper one, while the opposite should be the case between FRC and TLC. It has also been calculated that "airway closure" occurs in the right lateral position at volumes up to 50 % of TLC (33), therefore "airway closure" exists both at RV and at FRC in this body position and most of this closed off volume will probably be in the lower lung.

The wedge pressure increased more than the systolic pulmonary artery pressure both at RV and at FRC with the catheter wedged close to the diaphragm in the lower lung. The increase in perfusion of the lower lung at TLC as compared with at FRC also took place mainly in the diaphragmatic part of the lung, and is probably due to mechanical influences, e.g. decreased "airway closure" on the vessels in this lung region.

One of the main problems in this type of investigation is to secure open airways, for intrathoracic pressure changes have been shown to change the distribution of

pulmonary blood flow (7). Breath-holding with open glottis is commonly not difficult at FRC, while the glottis easily closes at RV and TLC. Each subject was instructed to keep his glottis open. In one group oesophageal pressure was measured and in a second group a pneumotachygraph was used to ascertain that airways remained open. The distribution of perfusion was the same regardless of monitoring methods, but in the group with pneumotachygraph an increase in $\dot{Q}$ was registered at TLC in the sitting position. This group was, however, too small to permit statistical evaluation. It is quite obvious that closure of the glottis late during breath-holding may change $\dot{Q}$ but not influence the regional distribution of blood as this is measured during the beginning of breath-holding. Otherwise $\dot{Q}$ did not change significantly between different lung volumes. Measurements of $\dot{Q}$ in relation to the regional distribution of blood are probably of limited value as the $^{133}\text{Xenon}$ will be distributed throughout the lung within 5 to 10 seconds, while the measurement of $\dot{Q}$ will span at least 20 to 25 seconds. Also, in all likelihood a "steady state" does not exist during these measurements.

Regional lung perfusion and central haemodynamics during hypoxia, hyperoxia and breath-holding (IV, V & VI)

I n t r o d u c t i o n

Hypoxia precipitated by breathing gas mixtures containing from 11 to 16 % oxygen (8, 18, 27) produces in the sitting position a more even pulmonary blood flow distribution. A review over the haemodynamic changes during hypoxia has been presented by Fishman (24), who states that hypoxia results in an increase in both pulmonary artery pressure and Q. Dugard & Naimark (22) have shown that in the anaesthetized erect dog, the increase in apical perfusion precipitated by hypoxia was well correlated to the increase in pulmonary artery pressure.

Hypoxia can also be incurred by breath-holding and since the lung bases are better perfused than the lung apices in the erect body position a preferential basal vasoconstriction, due to basal hypoxia, might thus develop (2). To achieve similar effects from breathing gas concentrations of about 10 % oxygen the rebreathing time should be held rather short, otherwise hypoxic vasoconstriction will develop in both the apical and in the basal regions. Arborelius (2) showed that when breathing 10 % oxygen in nitrogen with one lung and air with the other, the redistribution of blood began within one minute, and Doyle, Wilson & Warren (20) found that pulmonary artery pressure began to increase after about 1 minute of breathing 10 % oxygen in nitrogen.

Pure oxygen is known to lower pulmonary artery pressure in patients with increased pulmonary artery pressure

(12, 21, 40) and to change pulmonary blood flow distribution in patients with chronic obstructive lung disease (36, 37). However, in healthy man pure oxygen has been shown to have no effect on the pulmonary blood flow distribution (2, 17, 30). In supine subjects the mean pulmonary artery pressure did not decrease by more than 1 to 2 mm Hg and $\dot{Q}$ was unchanged (11, 47).

M a t e r i a l a n d m e t h o d s

Twenty-nine healthy subjects (six women age 19 - 36 and twenty-three men age 20 - 40) volunteered. The pulmonary blood flow distribution, the pulmonary artery pressure, the $\dot{Q}$ and the arterial blood gases were studied in the sitting body position during breath-holding at FRC, which was preceded by breath-holding at TLC for 40 to 60 seconds. Before breath-holding the subjects breathed either air or pure oxygen for 5 to 10 minutes. The effect of pure oxygen breathing for 5 minutes was also studied as well as the changes caused by breathing 10 % oxygen in nitrogen for one minute. Control values were obtained during breath-holding at FRC preceded by air breathing.

R e s u l t s a n d d i s c u s s i o n

Hypoxia, produced by rebreathing 10 % oxygen in nitrogen for 1 minute, gave a significant redistribution of blood towards the apices (IV & VI). The same type of redistribution has been described earlier, but with higher oxygen concentrations (11 to 16 % O_2) in the inspired gas and longer exposure (8, 18, 27).

The PaO_2 after 1 minute of 10 % oxygen breathing was about 50 mm Hg, which was obviously enough to precipitate hypoxic blood redistribution. In the sitting

position, ventilation per lung volume is higher at the lung bases as is oxygen uptake and thus if the hypoxic gas breathing period was sufficiently short, a preferential basal hypoxia could be produced. With a short breathing period the apical regions should not have time to reach a degree of hypoxia adequate to produce enough apical vasoconstriction to counteract further blood redistribution caused by basal vasoconstriction. This is supported by the fact that in earlier investigations where 10 to 12 % oxygen was breathed for 10 minutes or longer, the increase in pulmonary artery pressure was 5 to 10 mm Hg (20, 25, 43) whereas in the present investigation a mean increase of only 2 mm Hg was noted.

The $\dot{Q}$ also increased during hypoxia ($\bar{d} = 1.35$ litres per minute; $P < 0.005$). According to Fowler & Read (27) a redistribution of blood from the lower to the upper parts of the lung in the erect position can be explained by an increase in pulmonary artery pressure, due to generalized or preferential basal vasoconstriction or to an increase in $\dot{Q}$. Indirect estimation of left atrial pressure from wedge pressure indicated unchanged pressure during moderate degree of acute hypoxia (20, 55), and if an unchanged left atrial pressure of 5 mm Hg is assumed, a slight but insignificant increase in pulmonary vascular resistance was registered. It is also unlikely that the increase in pulmonary artery pressure could be caused by a generalized vasoconstriction, since the rather small observed pressure increase was inadequate to cause the measured redistribution of blood towards the apices (27). For these reasons an increase in $\dot{Q}$ in combination with a preferential basal vasoconstriction seems to be the most likely explanation for the re-

distribution of pulmonary blood flow towards the apices.

In most of the subjects the redistribution of blood during prolonged breath-holding was of about the same magnitude as that caused by hypoxia. The $\dot{Q}$ also increased during prolonged breath-holding ($\bar{d} = 1.51$ litres per minute; $P < 0.025$) to about the same extent as it did during hypoxia. The pulmonary artery pressure was doubled during breath-holding at TLC, which is in accordance with earlier findings (III). After exhalation to FRC the pressure decreased but still was significantly higher than during the control measurements ($\bar{d} = 4$ mm Hg; $P < 0.001$). The increase in pressure during breath-holding at TLC was thought to be due to a generalized increase in blood flow resistance throughout the lung (III). This presumed generalized increase in resistance may for unknown reasons persist even after exhalation to FRC and thus add to the pressure increase produced by hypoxia. This hypothesis was supported by the fact that when the experiment was repeated during 100 % oxygen breathing, the mean pulmonary artery pressure measured after exhalation to FRC was increased as compared to the control ($\bar{d} = 2$ mm Hg; $P < 0.01$), but significantly less ($\bar{d} = 2$ mm Hg; $P < 0.005$) than during air breathing.

It has been proposed (14) that low blood pH greatly influences the reactivity of the pulmonary vessels to hypoxia. In paper IV no direct correlation was found between blood pH and the reactivity to hypoxia, but the greatest redistribution was seen in the subject with the lowest pH and almost no response in the subject with the highest pH.

The PaO_2 decreased 18 mm Hg during breath-holding to

74 mm Hg (IV). Under these circumstances it seems quite likely that in the erect position the PaO_2 in the basal regions will be low enough to cause hypoxic vasoconstriction, which in turn should cause an increase in pulmonary vascular resistance and a more even blood flow distribution.

It then seems probable that the redistribution of blood both during short term hypoxia and at prolonged breath-holding during air breathing is mainly caused by the same mechanisms: a preferential basal vasoconstriction and an increase in $\dot{Q}$. This is also supported by the fact that most of the increase in $\dot{Q}$ goes to the apices. Both in absolute figures and in per cent the changes are greater in the apical area where the flow is almost doubled.

No basal hypoxia will develop during 100 % oxygen breathing, not even during prolonged breath-holding (V). The increase in pulmonary artery pressure was, as previously mentioned, less pronounced and probably caused by a general increase in resistance throughout the lung. It was not accompanied by any change in pulmonary blood flow distribution and there was no significant change in $\dot{Q}$.

The effect of 100 % oxygen breathing on the pulmonary blood flow in the sitting position was small. However, a significant ($P < 0.01$) increase in basal perfusion was evident when the pooled material from papers V and VI was statistically analysed. The $\dot{Q}$ and pulmonary artery pressure did not change significantly (VI), although the mean values were lower than the control. Similar results have been found in the sitting position (3), while in the supine position there was a decrease in pulmonary artery pressure only (11).

GENERAL SUMMARY

When the body position is changed from supine or prone to sitting there will be a decrease in apical perfusion. This decrease can be divided into one rapid and one slow phase. The rapid phase is thought to be due mainly to gravity and it occurred within 1 minute after sitting up. The slower phase was terminated within 20 minutes and was accompanied by a decrease in pulmonary artery pressure and $\dot{Q}$. The decrease in pulmonary artery pressure seems not only to be due to the decrease in $\dot{Q}$ but also to a decrease in pulmonary vascular resistance. After 20 minutes the pulmonary artery pressure tended to increase again without significant changes in $\dot{Q}$ and pulmonary blood flow distribution.

Pulmonary blood flow distribution in the sitting position was more even at RV than at FRC and TLC. Its relationship to the pulmonary artery pressure is illustrated by the fact that blood distribution was more even when the $^{133}\text{Xenon}$ was injected immediately after the exhalation to RV rather than after a delay when the pulmonary artery pressure was lower. Simultaneous registration of pulmonary artery pressure and wedge pressure at RV indicates that in the basal region, zones with higher pressure than pulmonary artery pressure develop. "Airway closure" is thought to be responsible for this pressure increase. The pulmonary artery pressure also increased at TLC without any increase in apical flow. This pressure increase is thought to be a result of a generalized increase in resistance throughout the lung.

In the right lateral body position the perfusion of the lowermost lung, specially at the diaphragm, was increased

at TLC as compared to at RV and FRC. Changes in pulmonary artery pressure influenced the distribution of perfusion little. The wedge pressure increased above the systolic pulmonary artery pressure both at RV and at FRC in the basal part of the lower of the two lungs. The perfusion of the lowermost lung thus seems to be highly sensitive to mechanical factors such as "airway closure".

In the sitting position short time hypoxia gave a more even blood flow distribution and an increase in pulmonary artery pressure and $\dot{Q}$. The redistribution is thought to be caused by a preferential basal vasoconstriction combined with an increase in $\dot{Q}$. The same mechanisms were also thought to be responsible for the more even blood flow distribution found during prolonged breath-holding. Prolonged breath-holding during 100 % oxygen breathing did not change the blood flow distribution, but a significant increase in pulmonary artery pressure was measured and is thought to be due to a generalized increase in pressure throughout the lung. Pure oxygen breathing in itself did not change pulmonary artery pressure and $\dot{Q}$ significantly, but an increase in basal perfusion was registered in most of the subjects.

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